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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 26	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 27	Oct 21	EVENTLINE has been reloaded
NEWS 28	Oct 24	BEILSTEIN adds new search fields
NEWS 29	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 30	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 31	Nov 18	DKILIT has been renamed APOLLIT
NEWS 32	Nov 25	More calculated properties added to REGISTRY
NEWS 33	Dec 02	TIBKAT will be removed from STN
NEWS 34	Dec 04	CSA files on STN
NEWS 35	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 36	Dec 17	TOXCENTER enhanced with additional content
NEWS 37	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 38	Dec 30	ISMEC no longer available
NEWS 39	Jan 21	NUTRACEUT offering one free connect hour in February 2003
NEWS 40	Jan 21	PHARMAML offering one free connect hour in February 2003
NEWS 41	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 42	Feb 13	CANCERLIT is no longer being updated
NEWS 43	Feb 24	METADEX enhancements
NEWS 44	Feb 24	PCTGEN now available on STN
NEWS 45	Feb 24	TEMA now available on STN
NEWS 46	Feb 26	NTIS now allows simultaneous left and right truncation

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NEWS 47   Feb 26   PCTFULL now contains images
NEWS 48   Mar 04   SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 49   Mar 19   APOLLIT offering free connect time in April 2003
NEWS 50   Mar 20   EVENTLINE will be removed from STN
NEWS 51   Mar 24   PATDPAFULL now available on STN
NEWS 52   Mar 24   Additional information for trade-named substances without
                   structures available in REGISTRY
NEWS 53   Mar 24   Indexing from 1957 to 1966 added to records in CA/CAPLUS

NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
              MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
              AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 2 April 2003 (20030402/ED)


=> s cyp2c19 and mephenytoin
          804 CYP2C19
          874 MEPHENYTOIN
L1        283 CYP2C19 AND MEPHENYTOIN

=> s l1 and (enantiomer? or racemic)
        18761 ENANTIOMER?
        17516 RACEMIC
            3 RACEMICS
        17516 RACEMIC
                (RACEMIC OR RACEMICS)
L2         41 L1 AND (ENANTIOMER? OR RACEMIC)

=> s l2 and (urine or plasma or saliva)
       116010 URINE
         1849 URINES
       116591 URINE
                (URINE OR URINES)
       477702 PLASMA
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          1974 PLASMAS
        478168 PLASMA
                 (PLASMA OR PLASMAS)
         17300 SALIVA
           226 SALIVAS
         17360 SALIVA
                 (SALIVA OR SALIVAS)
L3          23 L2 AND (URINE OR PLASMA OR SALIVA)

=> d l3 ibib, iabs 1-23
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L3 ANSWER 1 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2003:94916 BIOSIS
DOCUMENT NUMBER: PREV200300094916
TITLE: Stereoselective determination of the **CYP2C19** probe drug **mephenytoin** in human **urine** by gas chromatography-mass spectrometry.
AUTHOR(S): Nolin, Thomas D.; Frye, Reginald F. (1)
CORPORATE SOURCE: (1) School of Pharmacy, University of Pittsburgh, 807 Salk Hall, Pittsburgh, PA, 15261, USA: rfrye@pitt.edu USA
SOURCE: Journal of Chromatography B, (5 January 2003) Vol. 783, No. 1, pp. 265-271. print.
ISSN: 1387-2273.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:

A sensitive, specific and reproducible gas chromatographic assay utilizing mass-selective detection has been developed for the stereoselective determination of **mephenytoin** (MP) in human **urine**. Following extraction of **urine** samples using methyl tert.-butyl ether, separation of R- and S-MP was achieved with a chiral capillary column; detection and quantitation were accomplished by mass spectrometry in the single ion monitoring mode (m/z 104 and 189). Excellent linearity was observed for both **enantiomers** over the concentration range of 5-1000 ng/ml with corresponding correlation coefficients (r)>0.99. The intra- and inter-day precision and accuracy were within +-5%. This method employs a simplified processing procedure, demonstrates improved extraction recovery, and provides at least 5-fold greater sensitivity than previously reported assays. This method is well suited for the phenotypic evaluation of **CYP2C19** activity using **mephenytoin**.

L3 ANSWER 2 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:216118 BIOSIS
DOCUMENT NUMBER: PREV200100216118
TITLE: Stereoselective pharmacokinetics of pantoprazole, a proton pump inhibitor, in extensive and poor metabolizers of S-**mephenytoin**.
AUTHOR(S): Tanaka, Makoto (1); Ohkubo, Tadashi; Otani, Koichi; Suzuki, Akihito; Kaneko, Sunao; Sugawara, Kazunobu; Ryokawa, Yuichi; Ishizaki, Takashi
CORPORATE SOURCE: (1) Drug Metabolism and Physicochemical Property, Research Laboratory, Daiichi Pharmaceutical Co Ltd, 1-16-13 Kitakasai, Edogawa-ku, Tokyo, 134-8630 Japan
SOURCE: Clinical Pharmacology & Therapeutics, (March, 2001) Vol. 69, No. 3, pp. 108-113. print.
ISSN: 0009-9236.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:

Pantoprazole, a proton pump inhibitor, is administered as a **racemic** mixture. To determine the role of cytochrome P450 (CYP) 2C19 in the stereoselective metabolism of pantoprazole, we investigated the pharmacokinetic disposition of (+)- and (-)-pantoprazole in 7 extensive metabolizers and 7 poor metabolizers of S-**mephenytoin**. All of the subjects received an oral

40-mg dose of **racemic** pantoprazole as the enteric-coated formulation. In the extensive metabolizers, the mean clearance of (-)-pantoprazole was only slightly lower than that of (+)-pantoprazole and no significant differences in the other pharmacokinetic parameters between (+)- and (-)-pantoprazole were observed. The mean (+)/(-) ratios for maximum concentration, area under the ***plasma*** concentration-time curve from 0 to infinity, and elimination half-life were 0.94, 0.82, and 0.90, respectively. In contrast, in the poor metabolizers, the clearance values of both **enantiomers** were significantly lower than those in the extensive metabolizers, and a significant difference in pharmacokinetics between (+)- and (-)-pantoprazole was observed. The mean elimination half-life for (+)-pantoprazole was 3.55-fold longer than that of (-)-pantoprazole, and the mean maximum concentration and area under the ***plasma*** concentration-time curve from 0 to infinity for (+)-pantoprazole were 1.31- and 3.59-fold greater, respectively, than those for (-)-pantoprazole. These results indicate that the stereoselective metabolism of pantoprazole depends on S-**mephenytoin** 4'-hydroxylase (**CYP2C19**). The metabolism of (+)-pantoprazole was impaired to a greater extent than (-)-pantoprazole in the poor metabolizers.

L3 ANSWER 3 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:160131 BIOSIS
DOCUMENT NUMBER: PREV200100160131
TITLE: Phenotype analysis of cytochrome P450 2C19 in Chinese subjects with **mephenytoin** S/R **enantiomeric** ratio in **urine** measured by chiral GC.
AUTHOR(S): Yao, T. W.; Zeng, S. (1); Wang, T. W.; Chen, S. Q.
CORPORATE SOURCE: (1) College of Pharmaceutical Sciences, Zhejiang University, 353 Yanan Road, Hangzhou, Zhejiang, 310031: zengsu@yahoo.com China
SOURCE: Biomedical Chromatography, (February, 2001) Vol. 15, No. 1, pp. 9-13. print.
ISSN: 0269-3879.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
A chiral gas chromatographic method with FID was developed for the determination of S- and R-**mephenytoin** in human **urine**. The assay is linear from 25 to 800 ng/mL for each **enantiomer** and the limit of detection and limit of quantitation were 12 and 25ng/mL for each ***enantiomer*** , respectively. The method affords average recoveries of 74.41 +- 3.93% and 73.78 +- 3.02% for S- and R-**mephenytoin**, respectively. The method allows the phenotype study of **CYP2C19** in Chinese subjects. The phenotype pattern of 90 Chinese volunteers was determined, in which 26 volunteers received phenotyping and genotyping tests. The results of phenotype analysis showed that the interindividual variation was marked. The **mephenytoin** S/R **enantiomeric** ratios in ***urine*** of 11 volunteers were gtoreq0.95 and identified as poor metabolizers. The frequency of poor metabolizers was 12.2% in the Chinese subjects tested. A good relationship between phenotype and genotype analysis of ***CYP2C19*** was observed.

L3 ANSWER 4 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:466821 BIOSIS
DOCUMENT NUMBER: PREV200000466821
TITLE: Genetic polymorphism of CYP2D6 and **CYP2C19** metabolism determined by phenotyping Israeli ethnic groups.
AUTHOR(S): Britzi, Malka; Bialer, Meir; Arcavi, Lidia; Shachbari, Asmi; Kapitulnik, Jaime; Soback, Stefan (1)
CORPORATE SOURCE: (1) Kimron Veterinary Institute, 50250, Beit Dagan Israel
SOURCE: Therapeutic Drug Monitoring, (October, 2000) Vol. 22, No. 5, pp. 510-516. print.
ISSN: 0163-4356.
DOCUMENT TYPE: Article

LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Genetic polymorphism of the cytochrome P450 isoenzymes CYP2D6 and ***CYP2C19*** was determined by phenotyping four ethnic groups of the Israeli population. The groups consisted of Ethiopian subjects, Yemenite subjects, and Russian subjects representing first-generation new immigrants and an Israeli Arab group. Dextromethorphan was used as the probe for CYP2D6 activity and ***mephenytoin*** was used for **CYP2C19** activity. The two drugs were administered simultaneously and **urine** samples were collected over a period of 8 hours. The CYP2D6 phenotype was determined from the ratio of dextromethorphan conversion to dextrorphan and the **CYP2C19** phenotype from the ratio of S-**mephenytoin** and R-**mephenytoin**. The used liquid chromatographic method was able to completely separate dextrorphan and dextromethorphan. Fluorescence detection allowed dextromethorphan quantification at 1 ng/mL. **Mephenytoin enantiomers** were completely separated in high-performance liquid chromatography and the respective fractions were collected and analyzed using a gas chromatography/mass spectrometry system with selective ion monitoring. The prevalence of poor metabolizer phenotype of dextromethorphan (CYP2D6) in the Yemenite (0%) and Ethiopian groups (0%) was significantly different from the prevalence in the Russian (17%) and Israeli Arab (9%) groups. A significant difference was also found in the distribution of the metabolic ratio of the extensive metabolizer phenotype between the Ethiopian group and the Russian and Yemenite groups. No significant difference was found in the prevalence of poor ***mephenytoin*** metabolizer phenotype (**CYP2C19**) between the Yemenite (8%), Ethiopian (6%), Russian (9%), and Israeli Arab (8%) groups. No difference was observed in the distribution of metabolic ratio within the extensive metabolizer phenotype subgroups of the four ethnic groups.

L3 ANSWER 5 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:211564 BIOSIS
DOCUMENT NUMBER: PREV200000211564
TITLE: Steady state **plasma** levels of the **enantiomers** of trimipramine and of its metabolites in CYP2D6-, **CYP2C19**- and CYP3A4/5-phenotyped patients.
AUTHOR(S): Eap, Chin B. (1); Bender, Stefan; Gastpar, Markus; Fischer, Wilhelm; Haarmann, Caecilia; Powell, Kerry; Jonzier-Perey, Michele; Cochard, Nathalie; Baumann, Pierre
CORPORATE SOURCE: (1) Hopital de Cery, 1008, Prilly-Lausanne Switzerland
SOURCE: Therapeutic Drug Monitoring, (April, 2000) Vol. 22, No. 2, pp. 209-214.
ISSN: 0163-4356.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Steady state **plasma** concentrations of the (L)- and (D)-***enantiomers*** of trimipramine (TRI), desmethyltrimipramine (DTRI), 2-hydroxytrimipramine (TRIOH) and 2-hydroxydesmethyl-trimipramine (DTRIOH) were measured in 27 patients receiving between 300 and 400 mg/day **racemic** TRI. The patients were phenotyped with dextromethorphan and **mephenytoin**, and the 8-hour urinary ratios of dextromethorphan/dextrorphan, dextromethorphan/3-methoxymorphinan, and (S)-**mephenytoin**/(R)-***mephenytoin*** were used as markers of cytochrome P-450IID6 (CYP2D6), CYP3A4/5 and **CYP2C19** activities, respectively. One patient was a CYP2D6 and one was a **CYP2C19** poor metabolizer. A stereoselectivity in the metabolism of TRI has been found, with a preferential N-demethylation of (D)-TRI and a preferential hydroxylation of (L)-TRI. CYP2D6 appears to be involved in the 2-hydroxylation of (L)-TRI, (L)-DTRI and (D)-DTRI, but not of (D)-TRI, as significant correlations were measured between the dextromethorphan/dextrorphan ratios and the (L)-TRI/(L)-TRIOH ($r = 0.45$, $p = 0.019$), the (L)-DTRI/(L)-DTRIOH ($r = 0.47$, $p = 0.014$), and the (D)-DTRI/(D)-DTRIOH ($r = 0.51$, $p = 0.006$), but not with the (D)-TRI/(D)-TRIOH

ratios (r = 0.29, NS). **CYP2C19**, but not CYP2D6, appears to be involved in the demethylation pathway, with a stereoselectivity toward the (D)-***enantiomer*** of TRI, as a significant positive correlation was calculated between the **mephenytoin** (S)/(R) ratios and the concentrations to dose-to-weight ratios of (D)-TRI (r = 0.69, p = 0.00006). CYP3A4/5 appears to be involved in the metabolism of (L)-TRI to a presently not determined metabolite. The CYP2D6 poor metabolizer had the highest (L)-DTRI and (D)-DTRI concentrations to dose-to-weight ratios, and the **CYP2C19** poor metabolizer had the highest (L)-TRI and (D)-TRI concentrations to dose-to-weight ratios of the group.

L3 ANSWER 6 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:211554 BIOSIS
DOCUMENT NUMBER: PREV200000211554
TITLE: Is therapeutic drug monitoring a case for optimizing clinical outcome and avoiding interactions of the selective serotonin reuptake inhibitors.
AUTHOR(S): Rasmussen, Birgitte Buur (1); Brosen, Kim
CORPORATE SOURCE: (1) Clinical Pharmacology, Institute of Public Health, University of Southern Denmark - Odense University, Winslowparken 19, DK-5000, Odense C Denmark
SOURCE: Therapeutic Drug Monitoring, (April, 2000) Vol. 22, No. 2, pp. 143-154.
ISSN: 0163-4356.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
The selective serotonin reuptake inhibitors (SSRIs) comprise citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline and they differ from each other in chemical structure, by pharmacokinetic properties and, most importantly, with respect to enzyme-specific metabolism and interactions. Citalopram is administered as a **racemic** mixture. The drug is oxidated to desmethylcitalopram in the liver, partially by **CYP2C19** and partially by CYP3A4. Fluoxetine is administered as a racemate of R- and S-fluoxetine. Both R- and S-fluoxetine are metabolized by CYP2D6 to the active metabolites R- and S-norfluoxetine. Fluvoxamine is metabolized to inactive metabolites by CYP1A2 and CYP2D6. Paroxetine is metabolized to inactive metabolites partially by CYP2D6, and accordingly the metabolism of paroxetine is dependent on the genetic polymorphism of CYP2D6. Sertraline is metabolized to desmethylsertraline, probably by CYP3A4. Several analytical methods have been described for all SSRIs. Most assays are based on separation by high-performance liquid chromatography or gas chromatography. Stereoselective methods for the analysis of **racemic** citalopram and fluoxetine have been published. The SSRIs are generally well tolerated and their therapeutic indices are large. In several studies there has not been found a clear relationship between clinical efficacy and **plasma** concentration, nor any threshold that defines toxic concentrations. The available data do not suggest that any benefit be obtained from routine monitoring of SSRI ***plasma*** levels. Therefore therapeutic drug monitoring (TDM) of the SSRIs may be useful mainly in situations where poor compliance is suspected and when therapeutic failure or toxic events are experienced at clinically relevant dosages. Further, in special populations, such as in elderly patients, poor metabolizers of sparteine (CYP2D6) or **mephenytoin** (**CYP2C19**), and patients with liver impairment, the measurement of **plasma** concentrations may be useful.

L3 ANSWER 7 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:497070 BIOSIS
DOCUMENT NUMBER: PREV199900497070
TITLE: The phenotype and genotype analysis of S-**mephenytoin** hydroxylase (**CYP2C19**) in Chinese subjects.
AUTHOR(S): Yao Tongwei (1); Chen Shuqing (1); Wang Tongwen (1); Zeng Su (1); Ruan Hongqiang (1); Li Juhua (1)

CORPORATE SOURCE: (1) Department of Pharmaceutical Analysis, Zhejiang University, Hangzhou, 310031 China
SOURCE: Yaoxue Xuebao, (May 28, 1999) Vol. 34, No. 5, pp. 338-341. ISSN: 0513-4870.
DOCUMENT TYPE: Article
LANGUAGE: Chinese
SUMMARY LANGUAGE: Chinese; English
ABSTRACT:
AIM: To assess the phenotype and genotype pattern of S-**mephenytoin** 4'-hydroxylation in Chinese population. METHODS: The phenotypes of ninety healthy subjects were analyzed with S/R **mephenytoin** ratio in ***urine*** after an oral dose of 100 mg **racemic** ***mephenytoin*** by chiral GC-FID method. The genotypes of twenty-six among the 90 subjects were analyzed with identifying the wild-type(wt) gene and two mutations, CYP2C19m1 and CYP2C19m2 by PCR method. RESULTS: Of the 90 subjects eleven were identified as poor metabolizers with the S/R ratio of gtoreq0.95. Among the 26 genotyped subjects six were homozygous for wild-type (wt/wt); nine were homozygous for CYP2C19m1 (m1/m1); seven were heterozygous for the CYP2C19m1 (wt/m1); three were heterozygous for the CYP2C19m2 (wt/m2); one was the heterozygous for the two defects (m1/m2). CONCLUSION: The result of ***CYP2C19*** genotype analysis was in agreement with that of phenotype analysis. The frequency of PM by phenotype analysis was 12.2%.

L3 ANSWER 8 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:222498 BIOSIS
DOCUMENT NUMBER: PREV199900222498
TITLE: **CYP2C19** genotype does not represent a genetic predisposition in idiopathic systemic lupus erythematosus.
AUTHOR(S): Kortunay, Selim (1); Bozkurt, Atila; Bathum, Lise; Basci, Nursabah E.; Calguneri, Meral; Brosen, Kim; Kayaalp, S. Oguz
CORPORATE SOURCE: (1) Department of Pharmacology, Faculty of Medicine, Hacettepe University, 06100, Ankara Turkey
SOURCE: Annals of the Rheumatic Diseases, (March, 1999) Vol. 58, No. 3, pp. 182-185. ISSN: 0003-4967.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Background-The aetiology of systemic lupus erythematosus (SLE) is still unknown. In several cases, however, chemicals or drugs were identified as aetiological agents and associations with certain phenotypes of drug metabolising enzymes have been reported. The purpose of this study was to discover if there is an association between **CYP2C19** polymorphism and susceptibility to SLE. Methods-**Racemic mephenytoin** (100 mg orally) was given to healthy volunteers (n=161) and SLE patients (n=37) and then S-**mephenytoin** and R-**mephenytoin** were determined in eight hour **urine** samples. A 10 ml blood sample was obtained from healthy volunteers (n=80) and SLE patients (n=69) for genotypic assay. Each blood sample was tested for the detection of **CYP2C19***1 and ***CYP2C19*** *2 (formerly wt and m1 respectively) by oligonucleotide ligation assay. Results-The ratio of S/R-**mephenytoin** ranged from <0.1 to 1.293 in healthy subjects and from <0.1 to 1.067 in SLE patients. PM phenotype was observed in 2 of 37 patients with idiopathic SLE (5.4%) and 6 of 161 healthy subjects (3.7%). There were no significant differences in the frequency of PM phenotypes between the groups (Fisher's exact test, p = 0.64) or in the frequency distribution profiles of ratios of S-**mephenytoin** to R-***mephenytoin*** . No significant differences in distribution of overall genotypes and in allele frequencies were observed between the two groups. No significant relation was found between clinical features and the overall genotype. Conclusion-The results of this study indicate that **CYP2C19** genotype does not represent a genetic predisposition in idiopathic SLE patients.

L3 ANSWER 9 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:209864 BIOSIS
DOCUMENT NUMBER: PREV199900209864
TITLE: Phenotypic-genotypic analysis of **CYP2C19** in the Jewish Israeli population.
AUTHOR(S): Sviri, Sigal; Shpizen, Shoshi; Leitersdorf, Eran; Levy, Micha; Caraco, Yoseph (1)
CORPORATE SOURCE: (1) Clinical Pharmacology Unit, Division of Medicine, Hadassah University Hospital, Jerusalem, 91120 Israel
SOURCE: Clinical Pharmacology & Therapeutics, (March, 1999) Vol. 65, No. 3, pp. 275-282.
ISSN: 0009-9236.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Objectives: Evaluation of **CYP2C19** activity and the frequency of CUPSILONP2C19 alleles in the Jewish Israeli population. Methods: One hundred forty Jewish Israeli subjects received 100 mg **racemic** ***mephenytoin*** and collected **urine** for 8 hours. Urinary concentrations of **mephenytoin enantiomers** and 4'-hydroxymephenytoin were determined by gas-liquid chromatography and HPLC, respectively. **CYP2C19** activity was derived from urinary S/R-ratio and 8-hour urinary excretion of 4'-hydroxymephenytoin. Mutations were identified by polymerase chain reaction and enzyme digestion with SmaI (CUPSILONP2C19*2) and BamHI (CUPSILONP2C19*3). Results: Deficient **mephenytoin** hydroxylation was found in 4 subjects (2.9%; 95% confidence interval (CI), 0.1% to 5.7%) who were homozygous for CUPSILONP2C19*2. CUPSILONP2C19*2 was the major deactivating allele accounting for 15% (95% CI, 11% to 19%) of CUPSILONP2C19 alleles, whereas CUPSILONP2C19*3 was identified in 2 subjects (1%; 95% CI, 0% to 2%). Among 136 extensive metabolizers, 99 were homozygous for CUPSILONP2C19*1 and 37 were compound heterozygous CUPSILONP2C19*1/CUPSILONP2C19*2 (35 subjects) or CUPSILONP2C19*1/CUPSILONP2C19*3 (2 subjects). Gene dose effect was noted so that the S/R-ratio was significantly greater and urinary excretion of 4'-hydroxymephenytoin was significantly lower in compound heterozygous than in homozygous extensive metabolizers (0.310 +- 0.209 versus 0.225 +- 0.176, P < .04 and 48.6% +- 19.2% versus 56.3% +- 16.0%, P < .03, respectively). Female extensive metabolizers had a significantly lower excretion of 4'-hydroxymephenytoin than male extensive metabolizers (49.5% +- 17.6% versus 58.4% +- 16.7%, respectively, P < .005). Conclusion: The frequency of poor metabolizers of CUPSILONP2C19 and CUPSILONP2C19*2 allele in the Jewish Israeli population resembles findings in non-Asian populations. Complete concordance was noted between phenotypic and genotypic findings. CUPSILONP2C19 genotyping may enable subclassification of extensive metabolizers into subjects with high and low activity.

L3 ANSWER 10 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:27194 BIOSIS
DOCUMENT NUMBER: PREV199900027194
TITLE: Determination of S/R ratio of **mephenytoin** in human **urine** by chiral HPLC and ultraviolet detection and its comparison with gas chromatography.
AUTHOR(S): Huang, Song-Lin; Xie, Hong-Guang; Wei, Wang; Zhen-Hua, Xu; Chang-Hong, Jiang; Hong-Hao, Zhou (1)
CORPORATE SOURCE: (1) Pharmacogenetics Res. Inst., Hunan Med. Univ., Changsha 410078 China
SOURCE: Acta Pharmacologica Sinica, (Nov., 1998) Vol. 19, No. 6, pp. 548-550.
ISSN: 0253-9756.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English; Chinese
ABSTRACT:
AIM: To improve HPLC method for rapid determination of urinary S/R-ratio of ***mephenytoin*** , a widely used metabolic index for cytochrome P-450 2C19 (

CYP2C19) activity. METHODS: Aliquots of 0-8-h **urine** sample after dosing **racemic mephenytoin** 100 mg underwent one-step extraction with dichloromethane. Analysis was performed on a chiral column (250 mm X 4 mm, 5 mum) at lambda = 207 nm. The eluent was a mixture of acetonitrile and water containing both 0.1% glacial acetic acid and 0.2% triethylamine (14:86, vol/vol) at a flow-rate of 0.9 mL cntdot min-1. RESULTS: The ***enantiomers*** of **mephenytoin** in **urine** were well separated within 9 min. A linear correlation was observed between 50-5000 mugcntdotL-1 with the detection limit of 12.5 mugcntdotL-1 for both ***enantiomers*** of **mephenytoin**. This HPLC analysis was comparable to gas chromatography in accuracy and sensitivity, but with much shorter retention time and better resolution. CONCLUSION: The present HPLC method is good for rapid determination of the ability of subjects to hydrate S-***mephenytoin*** after oral administration of the **racemic** drug.

L3 ANSWER 11 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:403555 BIOSIS
DOCUMENT NUMBER: PREV199800403555
TITLE: Selective effect of liver disease on the activities of specific metabolizing enzymes: Investigation of cytochromes P450 2C19 and 2D6.
AUTHOR(S): Adedoyin, Adedayo; Arns, Patricia A.; Richards, W. O.; Wilkinson, Grant R.; Branch, Robert A. (1)
CORPORATE SOURCE: (1) Cent. Clin. Pharmacol., 623 Scaife Hall, Univ. Pittsburgh Med. Cent., 200 Lothrop St., Pittsburgh, PA 15213-2582 USA
SOURCE: Clinical Pharmacology & Therapeutics, (July, 1998) Vol. 64, No. 1, pp. 8-17.
ISSN: 0009-9236.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:
Background and Objectives. Drug metabolism is influenced by liver disease because of the central role that the liver plays in metabolic activities in the body. However, it is still unclear how activities of specific drug-metabolizing enzymes are influenced by the presence and severity of liver disease. As a consequence, alteration in metabolism of specific drugs cannot be easily predicted or appropriate dosage adjustment recommendations made. Methods. The activities of cytochromes P450 (CYP) 2C19 and 2D6 were investigated in a group of patients with mild or moderate liver disease (n = 18) and a group of healthy control subjects (n = 10). The disposition of **racemic** ***mephenytoin*** for **CYP2C19** and debrisoquine for CYP2D6 were characterized in **plasma** and **urine** samples collected over 192 hours. Results. The elimination of S-**mephenytoin** was severely reduced among patients with liver disease, resulting in a 79% decrease in ***plasma*** clearance for all patients combined. This reduction was related to the severity of disease, patients with moderate disease being affected more severely than patients with mild disease. Similar differences were observed in the urinary excretion of 4'-hydroxymephenytoin metabolite. By contrast, there was no effect on the disposition of R-**mephenytoin** or debrisoquine. Conclusion: These results show selectivity in the effect of liver disease on activities of specific metabolizing enzymes, **CYP2C19** being more sensitive than CYP2D6. They suggest that recommendations for modification in drug dosage in the presence of liver disease should be based on knowledge of the particular enzyme involved in metabolism of the drug. The results emphasize the need for further studies of each specific drug-metabolizing enzyme in the presence of liver disease.

L3 ANSWER 12 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:126056 BIOSIS
DOCUMENT NUMBER: PREV199800126056
TITLE: The induction effect of rifampicin on activity of **mephenytoin** 4'-hydroxylase related to M1 mutation of **CYP2C19** and gene dose.
AUTHOR(S): Feng, Hua-Jun; Huang, Song-Lin; Wang, Wei; Zhou, Hong-Hao

(1)
CORPORATE SOURCE: (1) Pharmacogenetics Res. Inst., Hunan Med. Univ., Changsha, Hunan 410078 China
SOURCE: British Journal of Clinical Pharmacology, (Jan., 1998) Vol. 45, No. 1, pp. 27-29.
ISSN: 0306-5251.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:
Aims: To determine the induction effect of rifampicin, on the activity of 4'-hydroxylase in poor metabolizers (PMs) with ml mutation of S-***mephenytoin*** 4'-hydroxylation and the relationship of the effect with gene dose. Methods: Seven extensive metabolizers (EMs) of S-**mephenytoin** 4'-hydroxylation, and five PMs with ml mutation were chosen to take rifampicin 300 mg day-1 orally for 22 days. Prior to and after rifampicin treatment, each subject was given **racemic mephenytoin** 100 mg. The 4'-hydroxymephenytoin (4'-OH-MP) excreted in the 0-24 h **urine** and ***mephenytoin*** S/R ratio in the 0-8 h **urine** were determined by h.p.l.c. and GC, respectively. Results: In all EMs, the excretion of 4'-OH-MP in the 0-24 h **urine** was increased by 146.4 +- 17.9%, 0-8 h urinary ***mephenytoin*** S/R ratio was decreased by 77.3 +- 8.8%, the percentage increase in the 0-24 h excretion of 4'-OH-MP in those **CYP2C19** homozygous (wt/wt) was greater than that in those heterozygous (wt/m, and wt/m2) (203.9 +- 42.5% vs 69.6 +- 4.1%). 0-8 h urinary **mephenytoin** S/R ratio of those PMs with m1 mutation was decreased by 9.6%, the amount of 4'-OH-MP excreted in the 0-24 h **urine** was increased by 80.1 +- 48.0%. Conclusions: The activity of 4'-hydroxylase of PMs with m1 mutation of S-***mephenytoin*** 4'-hydroxylation can be induced by rifampicin and the inducing effect of rifampicin on 4'-hydroxylase is gene dependent.

L3 ANSWER 13 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:502802 BIOSIS
DOCUMENT NUMBER: PREV199799802005
TITLE: An S-**mephenytoin** cysteine conjugate identified in **urine** of extensive but not of poor metabolizers of S-**mephenytoin**.
AUTHOR(S): Tybring, Gunnel (1); Nordin, Jan; Bergman, Tomas; Bertilsson, Leif
CORPORATE SOURCE: (1) Dep. Med. Lab. Sci. Technol., Div. Clin. Pharmacol., Karolinska Inst., Huddinge Univ. Hosp., SE-141 86 Huddinge Sweden
SOURCE: Pharmacogenetics, (1997) Vol. 7, No. 5, pp. 355-360.
ISSN: 0960-314X.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:
A conjugate of S-**mephenytoin** excreted in **urine** of extensive but not of poor metabolizers of S-**mephenytoin** has previously been reported. This conjugate, which is easily hydrolysed back to S-***mephenytoin*** , has now been isolated and identified in **urine** from one extensive metabolizer after a single dose of 100 mg **racemic** ***mephenytoin*** . High performance liquid chromatography purification, followed by gas chromatographic, mass spectrometric and amino acid analyses showed that the isolated compound is a cysteine conjugate of S-***mephenytoin*** . The significant mass spectrometric ions have been confirmed in three additional extensive metabolizers of S-**mephenytoin** , but were not detectable in **urine** from three poor metabolizer subjects. The exact structure of the conjugate is unknown, but we suggest that an S sbd N bond between cysteine and S-**mephenytoin** is formed via an oxidative radical mechanism catalyzed by **CYP2C19**.

L3 ANSWER 14 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:443784 BIOSIS
DOCUMENT NUMBER: PREV199799742987
TITLE: Enantioselective hydroxylation of omeprazole catalyzed by

CYP2C19 in Swedish white subjects.
AUTHOR(S): Tybring, Gunnel (1); Boettiger, Ylva; Widen,, Jolanta; Bertilsson, Leif
CORPORATE SOURCE: (1) Div. Clinical Pharmacology, Dep. Med. Lab. Sci. Technol., Huddinge Univ. Hosp., SE-141 86 Huddinge Sweden
SOURCE: Clinical Pharmacology & Therapeutics, (1997) Vol. 62, No. 2, pp. 129-137.
ISSN: 0009-9236.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:
Stereoselective disposition of omeprazole and its formed 5-hydroxy metabolite were studied in five poor metabolizers and five extensive metabolizers of S-***mephenytoin*** . After a single oral dose of omeprazole (20 mg), the ***plasma*** concentrations of the separate **enantiomers** of the parent drug and the 5-hydroxy metabolite were determined for 10 hours after drug intake. In poor metabolizers, the area under the **plasma** concentration versus time curve (AUC(0-8)) of (+)-omeprazole was larger and that of the 5-hydroxy metabolite of this **enantiomer** was smaller than the AUC(0-8) values in extensive metabolizers (p lt 0.001). The mean AUC(0-8) of the (-)-**enantiomer** of omeprazole was also higher in poor metabolizers than in extensive metabolizers, but only 3.1-fold compared with 7.5-fold for (+)-omeprazole. The rate of formation of the hydroxy metabolite from (-)-omeprazole was low and not significantly different in poor and extensive metabolizers. These results show that (+)-omeprazole is to a major extent hydroxylated by **CYP2C19**. Also (-)-omeprazole may partly be metabolized by this enzyme but is mainly metabolized by another enzyme, presumably CYP3A4, to the achiral sulfone metabolite. The **plasma** concentration ratio of omeprazole to 5-hydroxyomeprazole obtained 3 hours after the drug intake has been used to distinguish between extensive and poor metabolizer phenotypes. With use of the ratio between the (+)-***enantiomers*** of the parent drug and the metabolite, a better discrimination between phenotypes was obtained. The ratio between the (-)-***enantiomers*** also separated the phenotypes but was less discriminatory. For the future, measurement of total concentrations will suffice for phenotyping.

L3 ANSWER 15 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:320324 BIOSIS
DOCUMENT NUMBER: PREV199799610812
TITLE: Evidence for the effect of gender on activity of (S)-**mephenytoin** 4'-hydroxylase (**CYP2C19**) in a Chinese population.
AUTHOR(S): Xie, Hong-Guang; Huang, Song-Lin; Xu, Zhen-Hua; Xiao, Zhou-Sheng; He, Nan; Zhou, Hong-Hao (1)
CORPORATE SOURCE: (1) Pharmacogenetics Res. Inst., Human Medical Univ., Changsha, Hunan 410078 China
SOURCE: Pharmacogenetics, (1997) Vol. 7, No. 2, pp. 115-119.
ISSN: 0960-314X.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:
There is evidence that the sex-dependent expression of individual forms of the human cytochrome P450s (CYPs) results in gender-related differences in the hepatic metabolism of certain drugs. Previous work has shown that conflicting evidence exists relating to the sex differences in the activity of (S)-***mephenytoin*** 4'-hydroxylase (**CYP2C19**). Accordingly, we assessed the effect of gender on **CYP2C19** activity in a phenotyped and genotyped healthy unrelated Chinese population for further evidence of such a gender-based differentiation. One hundred and sixteen females and 129 males took one tablet of 100 mg racemic mephenytoin (Mesantoin, Sandoz) after emptying their urinary bladders. Amounts of (S)- and (R)-***mephenytoin*** and its metabolite 4'-hydroxymephenytoin (4'-OH-M) excreted in the postdose 0-8 h urine collection were determined by GC and HPLC methods, respectively. The **CYP2C19** activity was expressed as the

ratio of S/R-**mephenytoin** (S/R-ratio), the percentage of the dose excreted as 4'-OH-M (D%), and the log-10 of the hydroxylation index which was defined as the ratio of micromoles of (S)-**mephenytoin** dose to micromoles of 4'-OH-M excreted in **urine** (1g HI). From all the subjects studied, 53 extensive metabolizers (EMs) and 19 poor metabolizers (PMs) phenotyped were randomly selected and the DNA extracted from their blood samples was utilized for genotyping analysis according to the previously developed standard procedures. In this population, the phenotype PMs were identified in 10.9% (14/128) of the males, as compared with 11.2% (13/116) of the females (chi-2 = 0.0045, df = 1; p gt 0.05). In all phenotyped subjects, the S/R-ratio of EM males was significantly higher than that of EM females (mean +- SD; 0.28 +- 0.17 vs. 0.24 +- 0.15; p = 0.030), but no sexual differentiation was observed (p gt 0.05) in 4'-OH-M excreted among all EMs and PMs, or the S/R-ratio among all PMs. In all genotyped EMS, the frequency of homozygous EMs was 18.4% higher in females (51.7%, 15/29) than in males (33.3%, 8/24) although there was no significant difference (chi-2 = 1.1370, df = 1, p gt 0.05), but the S/R-ratio was lower in homozygous females than in homozygous males (0.22 +- 0.14 vs. 0.33 +- 0.09; p = 0.046). Thus, we conclude that the higher **CYP2C19** activity in females exists among both the phenotyped EMs and the genotyped homozygous EMs compared with that in males, and that the defect frequency of the enzyme activity is equal between the genders. We also conclude that the S/R-ratio is more a sensitive metabolic marker of ***CYP2C19*** enzyme activity than the D% and 1g HI.

L3 ANSWER 16 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:300473 BIOSIS
DOCUMENT NUMBER: PREV199799599676
TITLE: Metabolic disposition of lansoprazole in relation to the S-**mephenytoin** 4'-hydroxylation phenotype status.
AUTHOR(S): Sohn, Dong-Ryul (1); Kwon, Jun-Tack; Kim, Hyung-Kee; Ishizaki, Takashi
CORPORATE SOURCE: (1) Dep. Clinical Pharmacol., Soonchunhyang Univ. Coll. Med., Chonan 330-090 South Korea
SOURCE: Clinical Pharmacology & Therapeutics, (1997) Vol. 61, No. 5, pp. 574-582.
ISSN: 0009-9236.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:
Objective. To assess the possible involvement of **CYP2C19** in the metabolism of lansoprazole in vivo. Methods. Sixteen male Korean subjects, who had been phenotyped as extensive metabolizers and poor metabolizers of S-***mephenytoin*** 4'-hydroxylation polymorphism (n = 8 each) with ***racemic*** **mephenytoin** with use of the 8-hour **urine** analysis of 4'-hydroxymephenytoin, took an oral dose of 30 mg lansoprazole, and blood samples were collected up to 48 hours after dosing. Lansoprazole and its metabolites were measured by high-performance liquid chromatography with ultraviolet detection. Results. The mean lansoprazole area under the concentration-time curve (AUC), elimination half-life (t-1/2), and apparent oral clearance (CL-oral) were significantly (p lt 0.001) greater, longer, and lower, respectively, in the poor metabolizer than in the extensive metabolizer group. The mean values for the AUC of hydroxylansoprazole and AUC ratio of hydroxylansoprazole to lansoprazole were significantly (p lt 0.01 to p lt 0.001) less in the poor metabolizer than in the extensive metabolizer group, whereas those for the AUC of lansoprazole sulfone and ratio of lansoprazole sulfone to lansoprazole were greater (p lt 0.001) in the former than in the latter group. In addition, the log-10 4'-hydroxymephenytoin excreted in ***urine*** correlated significantly (p lt 0.01) with the CL-oral of lansoprazole. Conclusions. These results suggest that the hydroxylation of lansoprazole cosegregates with the genetically determined S-**mephenytoin** 4'-hydroxylation (**CYP2C19**) polymorphism in the Korean subjects.

L3 ANSWER 17 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:263658 BIOSIS
DOCUMENT NUMBER: PREV199799570261

TITLE: No correlation between side-chain of propranolol oxidation and S-**mephenytoin** 4'-hydroxylase activity.
AUTHOR(S): Xie Hong-Guang, Xu Zhen-Hua; Huang Song-Lin; Liu Jin-Hua; Wu Jin-Xiang; Jiang Chang-Hong; Zhou Hong-Hao (1)
CORPORATE SOURCE: (1) Pharmacogenetics Res. Inst., Hunan Med. Univ., Changsha 410078 China
SOURCE: Acta Pharmacologica Sinica, (1997) Vol. 18, No. 3, pp. 216-218.
ISSN: 0253-9756.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English; Chinese
ABSTRACT:
Aim: To determine if any correlation between the side-chain oxidative capacity for propranolol and S-**mephenytoin** 4'-hydroxylase (cytochrome P-450 2C19, **CYP2C19**) activity in healthy Chinese of Han nationality. METHODS: S-**mephenytoin** oxidative metabolite 4'-hydroxymephenytoin (4'-OH-M), S- and R-**mephenytoin**, and naphthoxylactic acid (NLA) excreted in **urine**, and propranolol in **plasma** were measured after 14 healthy extensive metabolizers of S-**mephenytoin** oxidation were given a single oral dose of **racemic mephenytoin** 100 mg and **racemic** propranolol 80 mg, respectively. S/R **mephenytoin** in **urine** was determined by chiral capillary gas chromatography with nitrogen-phosphorus detection, 4'-OH-M in **urine** by reversed-phase liquid chromatography (RPLC) with ultraviolet detection, and **plasma** propranolol or urinary NLA by the RPLC with fluorescence detection. RESULTS: No significant correlations were found between the partial metabolic clearance (Cl-m) of propranolol to NLA and 8 h urinary S/R ratio of **mephenytoin** (r-s = -0.0484; P = 0.8695), nor between the Cl-m and log-10 of 8 h urinary of 4'-OH-M (r-s = -0.1077; P = 0.7140). CONCLUSIONS: **CYP2C19** is not a principal P-450 isozyme responsible for the in vivo side-chain oxidation of propranolol in the Chinese.

L3 ANSWER 18 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:77914 BIOSIS
DOCUMENT NUMBER: PREV199799384617
TITLE: Non-response to citalopram in depressive patients: Pharmacokinetic and clinical consequences of a fluvoxamine augmentation.
AUTHOR(S): Bondolfi, G. (1); Chautems, C.; Rochat, B.; Bertschy, G.; Baumann, P.
CORPORATE SOURCE: (1) Serv. Hosp.-ambulatoire A, Clin. A, DUPA-Hopital de Cery, CH-1008 Prilly-Lausanne Switzerland
SOURCE: Psychopharmacology, (1996) Vol. 128, No. 4, pp. 421-425.
ISSN: 0033-3158.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:
The effect of comedication with fluvoxamine on the **plasma** concentrations of the **enantiomers** of citalopram and its metabolites in dextromethorphan/**mephenytoin** phenotyped patients pretreated with citalopram (CIT) was studied: seven female patients (45.1 +- 13.9 years) suffering from a major depressive episode (ICD-10: F-32.2 (n = 3 patients), F-33.2 (n = 2), F-32.10 (n = 1) or F-32.11 (n = 1)) , who were nonresponders to a 3-week treatment with 40 mg/day CIT (From day-21 to day 0) (day 0: MADRS score gtoreq 12), were comedicated for another 3 weeks with fluvoxamine (50 mg/day from day 1-7, 100 mg/day from day 14-21). All patients were extensive metabolizers of **mephenytoin** (**CYP2C19**) and dextromethorphan (CYP2D6), except one patient, who had a genetic deficiency of CYP2D6. There was a significant increase of the **plasma** concentrations of S- and R-citalopram from day 0 (27 +- 14 mu-g/l and 55 +- 23 mu-g/l, respectively) to day 21 (83 +- 38 mu-g/l and 98 +- 44 mu-g/l, respectively), after addition of fluvoxamine (P lt 0.02, for each comparison), and the mean ratio S/R-citalopram increased from 0.48 to 0.84. S-Citalopram inhibits more potently 5-HT uptake than R-citalopram: therefore, fluvoxamine increases the pharmacologically more

active S-citalopram with some stereoselectivity. According to a previous in vitro study, this pharmacokinetic interaction occurs on the level of ***CYP2C19*** , but also of CYP2D6 and CYP3A4 which, in contrast to CYP1A2, contribute to the N-demethylation of citalopram and which are stereoselectively inhibited by fluvoxamine. All but one patient showed clinical improvement by a decrease of the MADRS score by at least 50% and a final score ltoreq 13 (mean +- SD: day 0: 30.6 +- 9.2; day 21:11.0 +- 6.5). Some patients showed minor symptoms, such as nausea and tremor, but the combined treatment was generally well tolerated.

L3 ANSWER 19 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:77334 BIOSIS
DOCUMENT NUMBER: PREV199799384037
TITLE: Genotyping of S-**mephenytoin** 4'-hydroxylation in an extended Japanese population.
AUTHOR(S): Kubota, Takahiro; Chiba, Kan; Ishizaki, Takashi (1)
CORPORATE SOURCE: (1) Dep. Clinical Pharmacol., Res. Inst., International Med. Center, Japan, Toyama 1-21-2 Shinjuku-ku, Tokyo 162 Japan
SOURCE: Clinical Pharmacology & Therapeutics, (1996) Vol. 60, No. 6, pp. 661-666.
ISSN: 0009-9236.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:
Objective: To assess the genotype pattern of S-**mephenytoin** 4'-hydroxylation in an extended Japanese population. Methods: One hundred eighty-six unrelated, healthy Japanese subjects were genotyped for S-***mephenytoin*** 4'-hydroxylase (**CYP2C19**) according to a genotyping technique to identify the wild-type (wt) gene and two mutations, ***CYP2C19*** -m1 in exon 5 and **CYP2C19**-m2 in exon 4. Fourty-six of the 186 subjects genotyped were phenotyped with **racemic** ***mephenytoin*** using the conventional 8-hour **urine** analysis of 4'-hydroxymephenytoin. Results: The frequency of poor metabolizers by the genotyping analysis was 18.8% (35 of the 186 subjects), consisting of 12 homozygous for **CYP2C19**-m1 (m1/m1), three homozygous for ***CYP2C19*** -m2 (m2/m2), and 20 heterozygous for the two defects (m1/m2). Thus the allele frequencies of **CYP2C19**-m1 and **CYP2C19**-m2 were calculated to be 0.29 and 0.13 (107 and 46 of the total of 372 alleles), respectively. Among the 46 subjects phenotyped, seven were identified as the poor metabolizers, with a log-10 urinary excretion of 4'-hydroxyxnephenytoin of lt 0.3% of the **racemic** dose. These seven subjects were genotyped as the individuals with the m1/m1 (two), m1/m2 (four) or m2/m2 (one) allele combination, indicating a complete concordance between the phenotyping and genotyping tests. Conclusion: The present genotyping test confirmed that the frequency of **CYP2C19** mutant gene m1 is about 2.2 times greater than another mutant gene, m2, among Japanese poor metabolizers. The genotyping of ***CYP2C19*** discriminates between the two S-**mephenytoin** 4'-hydroxylation phenotypes completely in the Japanese subjects.

L3 ANSWER 20 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:541880 BIOSIS
DOCUMENT NUMBER: PREV199699264236
TITLE: Differences between white subjects and Chinese subjects in the in vivo inhibition of cytochrome P450s 2C19, 2D6, and 3A by omeprazole.
AUTHOR(S): Caraco, Joseph; Wilkinson, Grant R.; Wood, Alastair J. J. (1)
CORPORATE SOURCE: (1) Div. Clinical Pharmacology, Vanderbilt Univ. Sch. Med., Nashville, TN 37232-6602 USA
SOURCE: Clinical Pharmacology & Therapeutics, (1996) Vol. 60, No. 4, pp. 396-404.
ISSN: 0009-9236.
DOCUMENT TYPE: Article
LANGUAGE: English

ABSTRACT:
Objectives: To determine the effects of omeprazole on indexes of CYP2D6, ***CYP2C19*** and 3A in vivo activity and to compare these in white subjects and Chinese subjects. Methods: Omeprazole, 40 mg/day, or placebo were administered in a double-blind crossover study for 3 weeks to eight healthy white and seven Chinese male extensive metabolizers of **mephenytoin** and debrisoquin. Debrisoquin (10 mg), dapsone (100 mg), and **mephenytoin** (100 mg) were given 1 week before administration, on the last day of administration, and 3 weeks after administration, and **urine** was collected over 8 hours. Phenotypic trait values were obtained from the urinary recoveries of the probe drugs or their metabolites. Results: In the white subjects, omeprazole significantly inhibited **CYP2C19**-mediated S-***mephenytoin*** metabolism as indicated by decreases in the urinary R/S ***enantiomeric*** ratio (63% +- 13%; p lt 0.02; mean SD) and the excretion of 4'-hydroxymephenytoin (39% +- 13%; p lt 0.001). Similar but smaller changes were also noted in Chinese subjects, 22% +- 25% (p = 0.08) and 29% +- 13% (p lt 0.002), respectively. The interracial differences in the extent of inhibition of metabolism were statistically significant (p lt 0.01 and unaffected. The excretion of hydroxylamine dapsone-a putative probe of CYP3A activity-was reduced Conclusions: Omeprazole selectively inhibits the in vivo metabolism of S-**mephenytoin**, consistent with the ancestry. It is to be expected that similar situations would also occur when omeprazole is coadministered with other substrates of **CYP2C19**.

L3 ANSWER 21 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:508535 BIOSIS
DOCUMENT NUMBER: PREV199699230891
TITLE: **CYP2C19** genotyping and associated **mephenytoin** hydroxylation polymorphism in a Canadian Inuit population.
AUTHOR(S): Jurima-Romet, Malle (1); Goldstein, Joyce A.; Lebelle, Michel; Aubin, Remy A.; Foster, Brian C.; Walop, Wikke; Rode, Andris
CORPORATE SOURCE: (1) Bureau Drug Res., Drugs Directorate, Health Protection Branch, Health Canda, Banting Res. Centre 2201C, Tunney's Pasteur, Ottawa, ON K1A 0L2 Canada
SOURCE: Pharmacogenetics, (1996) Vol. 6, No. 4, pp. 329-339. ISSN: 0960-314X.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:
The **CYP2C19**-associated oxidation polymorphism of **mephenytoin** was investigated in an Inuit population living in the high Arctic of Canada. Results were obtained for 152 subjects, of whom 90 were unrelated to first degree relatives. Phenotyping was based on the capillary gas chromatographic determination of the S/R **enantiomeric** ratio in overnight ***urine*** collected after a dose of 100 mg (R,S)-**mephenytoin**. The phenotype was confirmed by determining the SIR **enantiomeric** ratio after acid treatment of **urine** samples, and for some subjects, by determining urinary recovery of 4'-hydroxymephenytoin using capillary electrophoresis analysis. DNA was analysed for the m1 and m2 mutations of ***CYP2C19*** . Three of 152 subjects (2.0%; 95% confidence limits: 0.0-4.2%) were phenotypically classified as poor metabolizers (PMs). Genotype analysis characterized three individuals as homozygous, and 28 individuals as heterozygous for the m1 mutation, the remaining individuals being homozygous for the wild-type allele. The genotype of the three PMs was concordant with that of the phenotype. DNA fingerprinting confirmed that these three individuals were genetically unrelated. The allele frequency of the ***CYP2C19*** -m1 mutation, determined in unrelated subjects, was 0.12 (95% confidence limits: 0.07-0.17). **CYP2C19**-m2 was not detected in this population. Thus, the Canadian Inuit resemble Caucasian rather than Asian populations in both the incidence of PM phenotype and the molecular basis of the polymorphism.

L3 ANSWER 22 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1995:458673 BIOSIS
DOCUMENT NUMBER: PREV199598472973
TITLE: Comparison of the interaction potential of a new proton pump inhibitor, E3810, versus omeprazole with diazepam in extensive and poor metabolizers of S-**mephenytoin** 4'-hydroxylation.
AUTHOR(S): Ishizaki, Takashi (1); Chiba, Kan; Manabe, Kyoko; Koyama, Eriko; Hayashi, Masahiro; Yasuda, Sanae; Horai, Yukio; Tomono, Yoshiro; Yamato, Chiyuki; Toyoki, Takaaki
CORPORATE SOURCE: (1) Dep. Clin. Pharmacol., Res. Inst., Int. Med. Cent. Jpn., Toyama 1-22-2, Shinjuku-ku, Tokyo 162 Japan
SOURCE: Clinical Pharmacology & Therapeutics, (1995) Vol. 58, No. 2, pp. 155-164.
ISSN: 0009-9236.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:
Objective: To compare the interaction potential of E3810, ((+-)-sodium 2-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methylsulfinyl)-1H-benzimidazole) a new proton pump inhibitor, and omeprazole with diazepam in relation to S-***mephenytoin*** 4'-hydroxylation status. Study design: Fifteen healthy male volunteers consisting of six poor metabolizers and nine extensive metabolizers of S-**mephenytoin** 4'-hydroxylation participated in the study, where two poor and three extensive metabolizers each as a group were randomly allocated to one of the three different treatment sequences with a 3-week washout period among the three trial phases. Each volunteer received an oral once-daily dose of E3810 (20 mg), omeprazole (20 mg), or placebo for 23 days and an intravenous dose (0.1 mg/kg) of diazepam on posttreatment day 8. ***Plasma*** concentrations of diazepam and demethyldiazepam were measured up to 16 days after the administration of diazepam. Results: Diazepam was more slowly metabolized in the poor metabolizers than in the extensive metabolizers. No significant effects of E3810 and omeprazole on any kinetic parameters of diazepam were observed in the poor metabolizers. In the extensive metabolizers, omeprazole significantly decreased the mean clearance of diazepam and increased its half-life, area under the **plasma** concentration-time curve, and mean residence time compared with E3810 and placebo (p lt 0.05 or 0.01), whereas no changes in these kinetic parameters were observed during the treatment with E3810. Omeprazole significantly increased the mean area under the **plasma** concentration-time curve (0-16 days) of demethyldiazepam in the extensive metabolizers compared with placebo (p lt 0.0 1), whereas E3810 significantly increased it in the poor metabolizers compared with omeprazole or placebo (p lt 0.05). Conclusion: The results indicate that E3810 as a substrate goes less toward S-**mephenytoin** 4'-hydroxylase (**CYP2C19**) and has a much weaker, if any, potential to interact with diazepam compared with omeprazole.

L3 ANSWER 23 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:350947 BIOSIS
DOCUMENT NUMBER: PREV199598365247
TITLE: Phenotyping of **CYP2C19** with enantiospecific HPLC-quantification of R- and S-**mephenytoin** and comparison with the intron4/exon5 G fwdarw A-splice site mutation.
AUTHOR(S): Brockmoeller, J. (1); Rost, K. L.; Gross, D.; Schenkel, A.; Roots, I.
CORPORATE SOURCE: (1) Institute of Clinical Pharmacology, Charite, Humboldt-University of Berlin, Schumannstrasse 20/21, D-10098 Berlin Germany
SOURCE: Pharmacogenetics, (1995) Vol. 5, No. 2, pp. 80-88.
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ABSTRACT:
S-**Mephenytoin** 4'-hydroxylase (**CYP2C19**) is a genetically polymorphic cytochrome P450. A modified method for **CYP2C19**

phenotyping was evaluated in 174 healthy German volunteers and the results were compared with genotyping for the intron4/exon5 G fwdarw A splice site mutation (ml) of **CYP2C19**, associated with the poor metabolizer (PM) phenotype. A smaller than usual test-dose of 50 mg (R,S)-**mephenytoin** was used and **urine** samples were collected from 0 to 5 h and from 5 to 8 h after administration. Trait measurements included the **mephenytoin** S/R ***enantiomeric*** ratio and the hydroxylation index (i.e. the molar ratio of 4'-hydroxy-**mephenytoin** urinary recovery to the administered S- ***mephenytoin*** dose). S- and R-**mephenytoin** were quantified by isocratic HPLC with a Chiraspher column and 80% n-hexane and 20% dioxane as the mobile phase. All individuals from whom DNA was available (n = 140, including six phenotypically identified PMs) were analysed for the ml mutation. The population frequency of this **CYP2C19** mutation was 0.15. Four individuals were homozygous for ml having S/R ratios of 0.9 or greater in both intervals of **urine** collection. Thus, individuals with an S/R ratio gtoreq 0.9 were classified as PMs and seven of all 174 phenotyped individuals were PMs (4%; 95% confidence limits: 1.6-8.1%). Heterozygous carriers of m-1 (n = 34) had a median SIR ratio (5-8 h **urine**) of 0.06 compared to 0.01 in individuals without this mutation (n = 102; p = 0.0005, Mann-Whitney U-test). No such gene-dose relation was apparent with the hydroxylation index. CYP2C9 may be involved in R-**mephenytoin** hydroxylation; thus, the Arg-144/Cys-144-polymorphism of CYP2C9 was determined (allele frequency of the Cys-144-variant: 0.13, n = 127). A major influence of this polymorphism on the recovery of R-**mephenytoin** was not detected. In summary, the proposed HPLC-method for S- and R-**enantiomers** of **mephenytoin** in 5-8 h **urine** samples reliably discriminates poor and extensive metabolizers of **CYP2C19** as confirmed by genotyping.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	49.36	49.57

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